siderations that is responsible for most of the failures in its application.

So often exercise occupies the borderland between education and therapeutics that it is not surprising if the lay educationalist is sometimes tempted on to the unknown land of the pathologist, to the discomfiture of his theories, and the physician too often fails to appreciate the range and effectiveness of this most powerful and versatile system of therapeutics which is always his to command.

THE PRESENT STATUS OF SERUM AND VACCINE THERAPY.[1]

By Mark Wyman Richardson, M.D.,
of Boston.

In the early nineties the study of the poisons of diphtheria and tetanus, and the successful production, through animal inoculation, of specific antidotes for those poisons, led not unnaturally to the hope, if not to the actual expectation, that a great principle had been discovered which should apply equally well to all bacterial disease. More than a decade has passed, however, and, speaking broadly, the great mass of bacterial disease remains outside the antitoxin category, and speculation has had to seek other theories to explain the immunity acquired after infection with organisms, such as typhoid and allied bacilli, the cholera spirillum and the various cocci.

Experiment soon showed that, in the fight against this class of organisms, nature directed her efforts, for the most part, against the bacteria themselves, and not, to any marked extent, against their toxins. An immense and valuable literature grew up covering the bactericidal and bacteriolytic sera (Pfeiffer). Strenuously opposed to this—the "humoral" school of the Germans—was the phagocytic school of the French, led by Metchnikoff. Each party claimed exclusive possession of the truth, but, as is commonly the case, time has shown that both have their proper spheres of influence, and, more recently, extracellular bacteriolysis has had to yield important ground to the specific opsonin and phagocytosis. Bacterial destruction, however whether it be by bacteriolysis or phagocytosis, is not without its disadvantages; it may be, in fact, a sort of double-edged sword, for disintegration of the invading organisms sets free their poisonous contents, and disastrous intoxication may be the result.

Until very recently there has been a sharp distinction drawn between these intracellular or endotoxins, seen in typhoid fever, cholera, dysentery, etc., and the extracellular toxins of diphtheria and tetanus. The bacilli of diphtheria and tetanus produced as a result of growth in a fluid medium a soluble toxin, which, when inoculated into a proper animal, caused the formation of a specific antitoxin; and this antitoxin united with and rendered inert definite amounts of toxin. The organisms of the second group, however, produced practically no toxin in fluid media. If disintegrated in any way, as by trituration when dry or frozen (liquid air), or by autolysis, they gave up their endotoxin. To this endotoxin, in animal experiments, could be produced a certain amount of toleration, but antitoxin production in any proper sense (obedience to the law of multiples) was not observed.

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[1] Read at a meeting of the Association of American Physicians, Washington, D. C., May 12 and 13, 1908.

Here again, however, clear-cut, diametrically opposed ideas have had to yield, and we now have good evidence that organisms, such as typhoid, dysentery, or plague, *can* produce soluble poisons, and that antitoxins of a moderate strength can be obtained.

In this connection it is interesting to note, too, that other possible means for rendering bacterial poisons innocuous are being suggested. Flexner, for instance, has pointed out the possibility that, in the process of opsonification and phagocytosis, the bacterial endotoxins might be broken up into less harmful compounds, and a condition of detoxication thereby brought about. Emmerich and Loewe, too, claim for their pyocyaneus enzymes the power, not only to kill diphtheria bacilli, but to neutralize their toxins.

Although the chief studies in immunity have had to do with bacteria and the infections produced by them, this field of research has been broadened very markedly in recent years, so that a great variety of animal and vegetable cells and poisons, with their corresponding antibodies, have been the subject of extensive investigation. Thus, we have hay fever antisera specific for certain vegetable pollens, antitoxins for snake venoms, and antisera for nearly every variety of animal cell, most important of which are the antitoxic and cytotoxic sera for hyperthyroidism.

Most of these antisera have been produced by inoculation of specific substances into the lower animals. The blood serum of these animals, when transferred to other animals and to man, have given varying degrees of passive immunity.

More recently the attempt has been made to do away with the animal inoculation, and by the direct incorporation of morbific material to protect actively the human individual against special disease, or if already sick to hasten his cure. This method of treatment with specific vaccines is one of very wide application and of great promise. Finally, the observed natural antagonism of one disease process for another has led empirically to the artificial induction of the one for the cure of the other. This antagonism is made use of in the treatment of sarcoma and leukemia by the toxins of streptococcus and bacillus prodigiosus (Coley). In the same category would be placed the treatment of diphtheria by the filtrates of pyocyaneus cultures—pyocyanase (Emmerich and Loewe).

NORMAL SERUM. Before taking up the question of specific immune sera in therapeutics, it will be well perhaps to consider briefly the uses to which simple normal blood serum has been put. Most important in studies upon bacteriolysis and hemolysis, as furnishing the digestive ferment or complement essential for the completion of those processes, fresh normal serum has not fulfilled the hopes once entertained for it as a therapeutic agent in bacterial disease, either alone or combined with specific antisera.

The most important use of fresh normal serum is seen, perhaps, in the prevention and cure of hemorrhage. This subject has been studied especially by Weil,[2] who finds that fresh blood serum is markedly efficacious in the prevention and cure of hemorrhagic dyscrasias associated with defective coagulation power. Much benefit has been seen in hemophilia, be it of the spontaneous or inherited type, in acute primary or secondary purpura with hematuria or hemarthrosis, or in severe anemias with a tendency to hemorrhage.

As a prophylactic measure when unavoidable operations are to be performed upon hemophiliacs, or when, as in jaundice, uncontrollable hemorrhage may be expected, the exhibition of fresh serum is of great service. It is given either intravenously or subcutaneously in doses of 15 to 30 c.c., and takes effect in twelve to twenty-four hours. Improved conditions persist one to three months. Human serum is most effective, but horse and rabbit sera are good. In default of other sera fresh diphtheria antitoxin can be used. Aside from its general use, local applications of serum to bleeding points or surfaces are said to exert marked styptic power.

Because, in animal experiment, injection of sterilized horse serum into the peritoneal cavity caused a marked determination of leukocytes toward the point of injection, with resulting increased resistance to infection with Bacillus coli and Staphylococcus pyogenes, Petit[3] has used this serum as a local application in more than 100 cases of human infection. Non-septic abdomens have been washed out with the serum to make them more resistant to possible infection, and already septic abdomens, septic uteri, and septic open wounds have been packed with gauze saturated with the serum with excellent results as to healing and cicatrization.

ACTINOMYCOSIS. Wynn[4] has treated a case of actinomycosis of the lung with a specific autogenous vaccine. A forty-eight-hour agar culture was heated to 60° C. for one hour. It was then ground up in an agate mortar and suspended in normal salt solution with 10 per cent. of glycerin; 1 c.c. of this suspension was equal to 1 mg. of "actinomycotin." Beginning with a dose of $\frac{1}{1000}$ mg., six inoculations were made in eleven weeks. General and local improvement was rapid, and patient was well one year after last inoculation.

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[2] International Clinics, Seventeenth Series, vol. iv.

[3] New York Med. Jour., June 22, 1907.

[4] Brit. Med. Jour., March 7, 1908.

ANTHRAX. Legge[5] collected 65 cases of anthrax with 2 deaths under treatment with a specific antiserum prepared according to Sclavo. The serum is produced by inoculation of asses first with bacterial vaccines, then with living cultures of increasing virulence. The serum is thought to be not especially antitoxic or bactericidal, but to act by stimulation of phagocytosis. The dose is 40 c.c. and is given subcutaneously. Marked improvement is seen in the patient's condition by the third day.

CANCER. Paine and Morgan[6] subjected Doyen's anticancer serum to critical tests, and found it entirely lacking in power, clinically and experimentally. Micrococcus neoformans, the cause of cancer, according to Doyen, and by the inoculation of which the anticancer serum was produced, was found by Paine and Morgan only rarely in malignant tumors, and then most presumably through some contamination. In animal experiment this organism produced no tumor formation; moreover, Doyen's own experimental tumors represented only inflammatory tissue.

CEREBROSPINAL MENINGITIS. In no disease has serum treatment made more advance in recent years than in cerebrospinal meningitis. Most important in this advance has been the work of Flexner[7] and his associates. Briefly, the serum is produced in horses by subcutaneous inoculation of dead cultures, living cultures, and autolysates of dead cultures. Many different strains of the meningococcus are used. After a year of immunization the serum of such a horse has been used intradurally after lumbar puncture in 130 cases, with 35 deaths, a mortality of 27 per cent. The dose is 20 to 30 c.c., and may be repeated daily for four to five days if necessary. When cases are treated within the first twenty-four hours the results are most brilliant.[8] The serum seems to act by stimulating phagocytosis, which destroys cocci and renders harmless their endotoxins.

Quite similar results have been seen in Germany. For instance, Levy,[9] using a serum prepared by Wassermann, had a death rate of only 11.76 per cent. in 17 cases in which the serum was given intradurally. In 14 untreated cases the mortality was 78 per cent. Very interesting is a case of cerebrospinal meningitis described by Peabody.[10] The infecting organism was, in this case, the streptococcus. Six intradural inoculations of streptococcus serum in doses of 10 c.c. each were given in eight days. After the second inoculation the spinal fluid became sterile and remained so. Clinically, the patient improved rapidly and recovered.

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[5] Brit. Med. Jour., 1905, vol. i.

[6] Med. Chir. Trans., London, 1906, 707.

[7] Flexner and Jobling. Jour. Exper. Med., 1908, No. 1.

[8] Dunn. Boston Med. and Surg. Jour., March 19, 1908.

[9] Deut. med. Woch., January 23, 1908.

[10] Med. Record, March 14, 1908.

This success with a streptococcic meningitis suggests immediately, of course, the treatment of other bacterial invasions of the meninges (pneumococcus or typhoid bacillus) with corresponding antisera. It is more than probable that such sera, although of doubtful value when given subcutaneously, might show valuable properties if applied in concentrated form at the very seat of infection.

Bacterial vaccines have been used in cerebrospinal meningitis with success by McKenzie[11] and by Rundle and Mottram,[12] but in the presence of such encouraging serumtherapy their use does not seem likely to be extensive. Unique is the experience of Radman,[13] who inoculated two patients subcutaneously with 8 c.c. of their own cerebrospinal exudate. No harm was done, and Radman thinks this form of specific therapy has a hopeful future.

CHOLERA. Haffkine[14] states that the incidence of the disease among the inoculated is one-tenth that of the uninoculated. The effect of the inoculation lasts fourteen months. If the disease is once contracted, however, the course and mortality is the same in the inoculated and the uninoculated. Effective antisera have not been developed.

INFECTION DUE TO THE COLON BACILLUS. Colon infections, especially those of the urinary tract, seem particularly favorable for vaccine treatment. Subjective improvement is oftentimes very striking. Pain and frequency of micturition are relieved quickly, and there is much general improvement. The character of the urine, however, changes but slowly, and complete elimination of bacteria from the urine is rare. Colon vaccines were used by Wright and Reid with success in two gall-bladder fistulæ after operation for gallstones. Vaccines have been used also with possible advantage after appendix operations.

DIPHTHERIA. Little new can be said on the subject of diphtheria antitoxin. It continues to be first and foremost of the anti-sera. The unbelievers become fewer every year. To the unconvinced, however, I would advise the study of a chart shown by Park in his Harvey lecture of 1905–1906. The mortality rate per 100,000 from diphtheria and croup in nineteen large cities of Europe, England, and the United States from 1878, to 1905, is here tabulated by years. The simultaneous reduction in the death rate from diphtheria and croup in all these widely separated cities since the introduction of antitoxin is most striking and gratifying (see chart).

The prophylactic benefits of antitoxin are well exemplified in a report of Terribile,[15] who made 2500 preventive inoculations in a recent epidemic. Of these, only 17 took the disease and none died. Comby[16] urges very strongly the use of frequent and large doses of antitoxin in case of diphtheritic paralysis, whether recent or old, light or severe, in child or adult. He repeats the injection every day for six days if necessary, and has cured all of 13 cases. Of these 13, 7 had antitoxin during the original disease, 6 had not. The methods of Park and his co-workers for the refinement of diphtheria antitoxin have been confirmed and very generally adopted.

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[11] Brit. Med. Jour., June 15, 1907.

[12] Lancet, July 27, 1907.

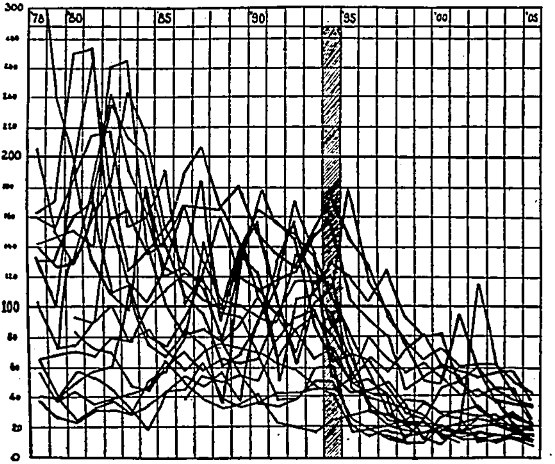
[13] Münch. med. Woch., July 4, 1907.

[14] Bull. de l'Inst. Pasteur, September 15 and 30, 1906.

[15] Gaz. degli Ospedali, Milan, xxviii.

[16] Bull. med., Paris, 1907, 442.

For a number of years Emmerich and Loewe have claimed marked bactericidal and antitoxic properties for their filtrates of cultures of Bacillus pyocyaneus. Very recently Mühsam[17] has investigated the substance, and substantiates in part the claims made for it. Experimentally, it does inhibit markedly the growth of diphtheria bacilli and many other bacteria. It seems also to neutralize in some way diphtheria toxin. Clinically the "pyocyanase" does no harm, and seems to digest the membrane in quite a remarkable manner. The fever is much decreased, and the general condition of the patient much improved. It is not to be used alone, but together with antitoxin.



Deaths per 100,000 from croup and diphtheria in nineteen large cities (1878–1905). (Park.)

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[17] Deut. med. Woch., February 6, 1908.

Bacillary Dysentery. Specific therapy has made a great deal of progress in this disease. Considerable confusion has arisen because of the varying types of bacillus found in different epidemics. The Shiga-Kruse variety has been found to be more virulent than the Flexner type and more efficient in the production of an antiserum. A polyvalent serum produced by inoculation with both types of bacilli has been suggested, and would seem to have the best outlook. The serum is both bactericidal and antitoxic. Good results cannot be expected unless the patient is injected with serum corresponding to the serum infecting organism. Bacteriological diagnosis is, therefore, very important, unless a polyvalent serum be available.

As to the efficacy of the serum, reports from Japan, Austria, France, Russia, and England agree in according it marked power. Shiga[18] treated 298 cases, with a death rate of 9 to 12 per cent. The length of the disease in those who recovered was twenty-five days; in those who died sixteen days. In 212 cases treated with drugs the mortality was 22 to 26 per cent. Those who recovered were sick forty days; those who died eleven days. In Russia Rosenthal gave serum treatment to 157 cases, with only 8 deaths—5.1 per cent.

Shiga inoculated 10,000 people in Japan with a mixture of dead bacilli and specific serum. The incidence of the disease was not much affected, but the mortality was reduced from 20 to 30 per cent. to practically nothing. Treatment of the original disease with specific vaccines has been tried in a few cases with success.

Erysipelas. Schorer[19] treated 37 cases of erysipelas with streptococcic vaccines (4 strains). The disease was apparently shortened somewhat, but immigration or recurrence was not prevented.

Exophthalmic Goitre. Bulkeley[20] reviewed all cases that had received specific treatment except those of Beebe and Rogers. This series numbered 86, of which 80 were benefited, 6 were not. In 16 cases the disease was probably cured. The substances used were thyroidectin, Moebius' serum, rodagen (dried milk powder of thyroidectomized animals), parathyroids of cows, milk of thyroidectomized goats, Murray's serum (animals fed with thyroid extract).

Beebe and Rogers[21] report 90 cases, of which 23 are regarded as cured, 52 improved, 11 not benefited, 4 died. Their serum, produced by intraperitoneal inoculation of Belgian hares with nucleoproteids and thyroglobulin from pathological and normal thyroids, exerts an antitoxic effect and also an inhibitory action upon cells of the glands.

Inasmuch as all writers agree that specific antithyroid therapy has been followed by beneficial results of greater or less degree, work along this line would seem to have a substantial basis, and much promise for the future.

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[18] Osler. Modern Medicine.

[19] Amer. Jour. Med. Sci., 1907, cxxxiv, p. 728.

[20] Boston Med. and Surg. Jour., 1907, p. 626.

[21] Jour. Amer. Med. Assoc., September 1, 1906.

GONORRHŒA. The treatment of the common infections of the urethra and conjunctiva by specific gonorrhœal sera and vaccines has not, thus far, met with much success. In certain secondary involvements, however, the outcome is more encouraging. Rogers and Torrey[22] report a series of 98 gonorrhœal joints treated with a polyvalent gonorrhœal serum; 80 per cent. of the cases were cured or much improved; 20 per cent. showed slight or no improvement. Not much can be hoped for in chronic cases with structural changes in the joints. Porter[23] had similar favorable results in 7 cases of gonorrhœal joints. He thinks the cases remarkably free from complicating disabilities. Moreover, the primary urethritis seemed to him to be favorably affected. Swinburne[24] was much impressed with the action of Rogers and Torrey's serum in 11 cases of gonorrhœal epididymitis. In 2 cases treatment was instituted very early (in 8 cases within twenty-four hours) and the course of the disease seemed to be remarkably modified and shortened.

The use of specific vaccines in gonorrhœal joints has been followed in most instances by favorable reports. Cole and Meakins,[25] in an experience with 15 cases, thought distinct benefit was conferred by inoculation. At the Massachusetts General Hospital Dr. H. F. Hartwell has treated 31 cases (as yet unpublished) with encouraging results. In a personal communication Dr. Hartwell says: "There were 31 gonorrhœal joints, 14 acute, 17 subacute and chronic. In 11 cases the gonococcus was obtained from the urethra and grown in pure culture. In 3 cases cultures were made from the joint, with 1 positive result. In 14 acute cases, the average time from beginning treatment until resuming work was six to seven weeks; the shortest three, the longest twenty and one-half weeks. In addition to vaccines, they had fixation while the acute symptoms lasted, and some had baking and massage. All but 3 obtained complete motion in the affected joints; 2 of these were infections of the right wrist and hand, and in both motion in the wrist is limited by adhesions. In 1, an infection of the metacarpophalangeal joint, stiffness persisted. These 3 cases were treated with stock vaccine. In the 17 subacute and chronic cases disability in the joints had existed for periods varying from three weeks to two years. The average duration of treatment was 5.9 weeks, the shortest one and one-half, longest twelve and one-half weeks. In some cases passive motion on Zander machines was used. All were discharged with good functionating joints. One case, in addition to multiple subacute joints, had adhesions in both hips, the result of a previous infection. Treatment had no effect on adhesions. It seems doubtful if vaccines had any influence on shortening the acute symptoms, although the variation in the individual infection makes this difficult to determine. In chronic joints response to treatment was more obvious, and cases which had been obstinate for a long time seemed to clear up more rapidly under vaccine treatment. No appreciable effect was noted in lessening the urethral discharge."

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[22] Jour. Amer. Med. Assoc., September 14, 1907.

[23] Jour. Royal Army Med. Corps, 1907, p. 513.

[24] Jour. Amer. Med. Assoc., 1907, 319.

[25] John Hopkins Hosp. Bull., June to July, 1907.

Somewhat exceptionally Butler and Long[26] had marked success in the treatment of vulvovaginitis in children with gonorrhœal vaccines. Most of the cases had been doing badly on routine treatment. The results of vaccine treatment were much more sharp and definite. The patients' stay in the hospital was shortened. Two cases which had not improved on a monovalent vaccine, improved rapidly when a polyvalent vaccine was substituted.

Altogether, the outcome for specific treatment in gonorrhœa, in some of its phases at least, is distinctly hopeful. If vaccines will accomplish as much as sera, the question will, of course, be much simplified.

HAY FEVER. The report of Curtis[27] shows that there is anything but unanimity among specialists as to the therapeutic value of pollantin. Curtis says that "in response to 300 inquiries of specialists, the great majority states that, without the removal of ridges, spurs, etc., the treatment has been unsatisfactory." Knight,[28] on the other hand, who collected 219 cases from 81 physicians, found that 52 per cent. of the cases were effectively benefited; 30 per cent. partially benefited; 18 per cent. not benefited.

LEPROSY. In an effort to influence favorably the course of leprosy a number of different substances have been made use of. Among these may be mentioned tuberculin, diphtheria antitoxin, anti-snake venom, and sera produced by inoculation into animals of ground-up leprous nodules.

More recently Rost,[29] of the Indian Medical Service, has inoculated 124 cases with the filtrates of a six-months-old culture of the leprosy bacillus upon a special medium. Fourteen cases have been cured. The others have shown marked improvement.

Deycke[30] has isolated from leprous nodules what he calls *Streptothrix leproides*. Extraction of this with ether gives a neutral fat which he calls "nastin." Combined with benzoyl chloride, nastin becomes much more powerful, and injected into patients causes a reaction quite similar to the tuberculin reaction. After inoculations the lepra bacilli in the nodules show marked degeneration and bacteriolysis. Results upon 40 patients give Deycke much encouragement.

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[26] Jour. Amer. Med. Assoc., March 7, 1908.

[27] Ibid., July 13, 1907.

[28] Med. Record, March 10, 1906.

[29] Ref. to by Dyer, Osler's Modern Medicine.

[30] Brit. Med. Jour., April 4, 1908.

LEUKEMIA. Samson[31] reports a case of a child with lymphatic leukemia, in which the leukemic signs and symptoms completely disappeared during an intercurrent attack of noma. After the subsidence of the noma, however, the leukemic condition recurred and the child died.

Larrabee[32] has treated 4 cases of leukemia with the mixed toxins of streptococcus and Bacillus prodigiosus (Coley). The first case was that of the splenomyelogenous type and was greatly improved. Of three lymphatic leukemias, one was slightly improved and two not improved.

Personally, I have used these toxins in one case of lymphatic leukemia in its last stage. Coincidently with the inoculation the glandular enlargements decreased, as did also the size of the spleen. The blood picture also improved a good deal. The patient, however, lost strength steadily, and finally succumbed to an intercurrent pneumonia.

PLAGUE. Haffkine[33] states that among 639,630 uninoculated persons there occurred 49,433 cases of plague (7.7 per cent.), with 29,733 deaths (4.7 per cent.). Of 186,797 who had been inoculated with plague vaccine, 3399 (1.8 per cent.) took the disease and 814 (0.4 per cent.) died. Production of immunity is quite rapid; so much so that Haffkine believes that vaccines used very early in the disease can be of service in aborting it. As to serum treatment, Bannermann and Terni compared 1014 cases treated with four kinds of serum with 1020 untreated cases, and found the mortality practically the same. Early treatment is very important. Choksy, who has had large experience, had, in private practice, a death rate of 40 per cent., as compared with 62 per cent. in hospital cases which came under treatment on the average much later.

PNEUMONIA. Anti-pneumococcic serum has been used by a number of clinicians here and abroad. Individuals have been enthusiastic in its praise, but the consensus of opinion is against its having any marked therapeutic value. Treatment with specific vaccines has been tried by Wolf[34] in 14 cases, with 3 deaths (27.2 per cent). The mortality in untreated cases for the same epidemic was 40 per cent. Vaccination was followed by rise in the opsonic index, and crisis occurred in those who recovered within eighteen hours in all cases except one. Five cases had crisis on the third day; 3 on the fourth; 1 on the fifth; 2 on the sixth day. Further investigation along these lines would seem to be indicated.

Empyema due to the pneumococcus has seemed in the hands of a number of observers to be especially amenable to vaccine treatment.

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[31] Berl. klin. Woch., February 3, 1908.

[32] Boston Med. and Surg. Jour., February 6, 1908.

[33] Bull. de l'Inst. Pasteur, October 30, 1906.

[34] Jour. Infect. Dis., 1906, p. 739.

SARCOMA. Coley,[35] in his recent report on the treatment of sarcoma with the toxins of streptococcus and Bacillus prodigiosus, says that to date, in 47 personal cases and 100 of other surgeons, the tumors have completely disappeared. In 28 personal cases and 30 of other physicians there has been no recurrence for a period of three years. Among his personal cases there were sarcomas of every kind but melanotic. In a majority of instances the diagnosis was confirmed by pathologists of the first class.

STAPHYLOCOCCIC INFECTION. As is well known, results in staphylococcic infections treated with specific vaccines have been more encouraging than in any other variety of bacterial invasion. Opinion is practically unanimous that acne, boils, carbuncles, sycosis, fununculosis, etc., are very favorably influenced. Whether general blood invasion with its high mortality can be controlled remains to be seen. Early blood cultures must become, in these cases of general sepsis from whatever germ, more a matter of course, for in this way only do early diagnosis and early specific treatment with autogenous vaccines become possible.

STREPTOCOCCIC INFECTIONS. The question of streptococcic infections, sera, and vaccines is still very confused. The differences in race and virulence of various streptococci makes the study of immunity most difficult. In all the discussions, however, polyvalence, be it of serum or vaccine, is an acknowledged point of great importance. Treatment, furthermore, must be begun at the earliest possible moment. Statistics are unsatisfactory, but the general impression is that specific therapy does good. Generally speaking, local infections have done the best.

The recent literature shows, however, a number of cases of general streptococcic sepsis treated successfully with autogenous vaccines. No harm has been done apparently, and the method should surely be tested.

Most interesting and encouraging has been the study on scarlet fever and its relation to the streptococcus. Work by Gabritschewsky and other Russians has emphasized the important role played by the streptococcus in scarlet fever. They point out that the streptococcus is present in many scarlet fever throats; that streptococcus vaccines cause scarlatiniform eruptions; that complement deviation shows streptococcus amboceptors in scarlet fever blood; that the mortality in scarlet fever has been markedly reduced by the use of a serum produced by inoculation of a scarlet fever streptococcus (Moser); and finally, that by inoculation of streptococcus vaccines efficient prophylaxis against scarlet fever has been secured.

SNAKE VENOMS. Early in his studies upon snake venoms and their antidotes Calmette thought that anticobra serum would be efficient against other venoms as well. More recent work, however, by Lamb, also by Flexner and Noguchi, has shown that antivenoms are highly if not absolutely specific. To be of any practical value, therefore, a protective serum will have to be polyvalent.

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[35] Bost. Med. and Surg. Jour., February 6, 1908.

TETANUS. There is practically no dissent from the view that tetanus antitoxin is all powerful in prophylaxis. It must be given as early as possible. The greater the delay the larger the dose should should be. As to treatment of the declared disease opinions differ. One observer has said that "light cases get well without serum, and severe cases die with it."

Brandenstein[36] treated 20 cases with serum subcutaneously, with 16 deaths—mortality 80 per cent. Hoffmann[37] treated 13 cases subcutaneously, with 7 deaths—53.8 per cent. Of 16 cases, however, in which serum was injected intradurally, only 2 died. One of these died from a complicating pneumonia. The other was very weak after amputation of an arm for sarcoma, and would have died anyhow in all probability. Discarding these 2 cases, Hoffmann has, with intradural inoculation of serum, a clean slate of 14 cases with no deaths.

TUBERCULOSIS. Through ignorance of its dangers, specific therapy in tuberculosis received in its infancy a setback which it has taken years for it to recover from. Gradually, however, its laws and limitations have become better known and its great value is now recognized the world over. The favorable opinion refers now especially to active immunization produced by direct inoculation of the tubercle bacillus or its products.

It makes little difference apparently what variety of tuberculin is used. More depends upon the method and skill of the physician. Inasmuch as, in animal experimentation, inoculation with the living bacillus produces the strongest immunity, we should, theoretically at least, aim to approach, as nearly as possible, these conditions in human treatment. This would be secured approximately by a combination of living filtrate (Tuberculin B. F. of Denys) with bacillary emulsion (Tuberculin B. E. of Koch). Corresponding tuberculins of the bovine type are much used by Spengler, who claims that there is a mutual antagonism between the two varieties of bacilli and their pathological processes. Thus, he says, pulmonary tuberculosis is the result of infection with the human types of bacillus and must be treated with bovine tuberculin, whereas, tuberculosis of bones, joints, and glands, being due to bovine bacilli, is best treated with human tuberculin. Be that as it may, bovine tuberculins may be tried in those cases which do not improve on the human varieties.

The whole question of tuberculin treatment has been much clarified through the work of Denys and Trudeau, and has been well summed up by Ringer in the dicta that "time and tolerance" are the essential things, and that the word "haste" has no place in treatment with tuberculins. Although in the past a careful selection of cases for tuberculin treatment has been deemed essential, the opinion seems to grow that practically any case can be inoculated if sufficient care be exercised.

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[36] Deut. Zeit. f. Chir., vol. xcii.

[37] Beit. zür klin. Chir., October, vol. lv.

Allen[38] has recommended in tuberculosis a vaccine made from tuberculous sputum. Such a vaccine has a number of theoretical advantages. It is a mixed vaccine, contains primary and secondary invaders, the bacteria concerned are autogenous, and their fighting powers have not been diminished by artificial cultivation.

Specific antisera have been used especially in Europe. The best known are those of Marmorek and Maragliano. Opinions of these in their own countries have been, on the whole, favorable, but as tried in this country, at the Phipps Institute and at Saranac, the results have shown them to be of doubtful value.

TYPHOID FEVER. *Prophylaxis.* As a result of specific inoculation of large numbers of troops in the British Army the following results were obtained by Wright: Of 1758 inoculated, 142 died (8 per cent.). Of the uninoculated, of whom there were 10,980 under the same general conditions, 1800 died (16.6 per cent.). The incidence of the disease in the various squadrons was anywhere from two- to twenty-eight-fold greater in the uninoculated than in the inoculated. As an inoculating fluid Wright used dead cultures. Two doses should be given to secure the best results. The only disadvantage of the procedure seemed to be that inoculation is followed by a short period of hypersusceptibility to infection. Increased immunity seems to last from one to three years.

The experience of the Germans with antityphoid inoculation has not been so extensive, but in the main confirms Wright's results.[39] Of 424 typhoids, 324 had not been inoculated. In the uninoculated the mortality was 11.9 per cent.; in the inoculated, 4 per cent. In the inoculated the disease was milder and there were fewer complications and relapses.

In the treatment of typhoid fever no one has approached, in experience or success, Chantemesse[40] in Paris. With his colleagues he has treated 1000 cases, with a death rate of 4.3 per cent. Of 5621 cases who were given routine treatment during the same period, 17 per cent. died. Of patients who were given serum treatment before the seventh day Chantemesse lost not a single one. The nature of Chantemesse's serum is difficult to understand. He speaks of it as antitoxic and as produced by inoculation of horses with a true typhoid toxin. It does not, however, act directly upon the toxin, as does the diphtheria antitoxin, but in some way indirectly. It stimulates the spleen, bone marrow, and other lymphatic apparatus to increased opsonin production. The sicker the individual the smaller must be the dose, lest too many bacilli be destroyed at once. There would seem to be, therefore, a strong bactericidal element in the serum. The serum treatment is combined with the cold bath treatment, and calcium chloride is given as a routine measure to prevent hemorrhage. Chantemesse's results have been confirmed to a certain extent by the Germans, and von Leyden[41] reports 3 cases treated with antitoxic serum prepared by Meyer and Bergell.[42] These cases were all remarkably short, having normal temperatures on the sixteenth, seventeenth, and nineteenth days. The serum is said to be of only moderate strength and to be both bacteriolytic and antitoxic. In this connection it is important to bear in mind, as suggested by von Stenitzer, that an antitoxin, although weak, as in dysentery, may be of great service in tiding over critical cases.

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[38] Jour. Amer. Med. Assoc., July 20, 1907.

[39] See Morgenroth in Kolle u. Wassermann's Handbuch der pathogenen Mikro-organismen Ergaensung's Band, No. 1, S. 234.

[40] Hygiene gén. et appliqué, Paris, 1907, 577.

Personally, I have treated 132 cases of typhoid fever with specific typhoid products,[43] serum, bouillon filtrates, and the non-toxic residue of the typhoid bacillus as prepared by Professor Vaughan, of Ann Arbor. The results were largely negative, with one exception. By continued inoculation during convalescence of the non-toxic residue the occurrence of relapses was cut down apparently from 22 to 5 per cent.

Very recently I have treated 2 cases with autogenous vaccines. One case was quite severe, with marked mental and renal involvement. He received about 40,000,000 dead bacilli daily under the skin for two and one-half weeks. There was steady though slow improvement. The second case was the earliest and mildest I have ever seen. Daily inoculations with 25,000,000 to 50,000,000 autogenous vaccines was followed by rapid fall in temperature, which reached normal on the sixteenth day. This case emphasizes the fact that in typhoid, as in other infectious processes, specific treatment, to be effective, must begin early. Hospital cases, in my experience, do not come in on the average until the end of the second week. Lack of positive diagnosis also entails oftentimes further delay.

In the future, however, with the more general use of blood cultures, early diagnosis and earlier specific treatment will be possible, and the results, I am sure, better.

Theoretical considerations and personal experience lead me to believe that in any treatment of typhoid fever with bacterial products (and this idea applies to other infectious processes as well) we might get more favorable results if we combined dead bacilli with the filtrate of living cultures, for such a combination would approximate more nearly to inoculation with the living organism.

I have found typhoid patients infinitely more sensitive to living filtrates than to any of the devitalized bacillary substances, and I feel certain that the degree of heat necessary to kill the bacilli destroys other products of growth which may be very essential to the production of rapid immunity.

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[41] Med. Klin., August 4, 1907.

[42] Berl. klin. Woch., May 6, 1907.

[43] Boston Med. and Surg. Jour., October 3, 1907.

This point is, of course, not new. It has already received attention in tuberculosis, in the recommended use of tuberculin B. F. either alone or combined with tuberculin B. E.

As to the value of the opsonic index as a guide for the use of vaccines, the opinion has steadily gained ground that the index is so unreliable as not to justify the amount of time and trouble necessary for its determination.

THE PARAVERTEBRAL TRIANGLE OF DULNESS (GROCCO'S SIGN) IN PREGNANCY.

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It has been satisfactorily demonstrated by Grocco,[1] Rauchfuss,[2] Thayer and Fabyan,[3] Ewart,[4] Frankenheimer,[5] and others that when there is a collection of fluid in one pleural sac dulness on the opposite side of the spine may be percussed. This dulness is roughly of triangular outline, and is so placed that the spinal column forms its vertical side. It has also been frequently demonstrated that in conditions other than simple collections of fluid in the pleural sac paravertebral dulness may be obtained. This is particularly the case in lobar pneumonia, when the consolidation lies along or near the spine, and in various newgrowths when the tissues of the mediastinum are involved. The paravertebral area of dulness in these cases rarely has the distinct triangular form that is so well marked in pleural effusion. Other characteristics, such as variations in size and shape of the paravertebral dulness, voice and breath sounds over and adjacent to the triangle, etc., may be wanting.

Recently several observers have reported cases in which it was possible to obtain a paravertebral dulness in conditions in which the affections were extrathoracic. Ewart[6] mentions that dulness may be percussed along the spine in ascites; Beall[7] gives details of a well-delimited paravertebral triangle on the left side in a case of subphrenic abscess, and a short time ago I called attention to

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[1] Rivista crit. di clinica med., 1902, Nos. 13 and 14.

[2] Deut. Archiv f. klin. Med., 1906, lxxxiv, 186.

[3] Amer. Jour. Med. Sci., January, 1907.

[4] Lancet, 1907, ii, 49, 189.

[5] California State Jour. Med., 1907, v, 224.

[6] Lancet, 1907, ii, 189.

[7] Jour. Amer. Med. Assoc., 1907, xlix, 2148.